

oligonucleotide(s) are substituted with other nucleotide bases, so called universal bases, which bind to thymidine (T) but lack the ability to activate adenosine receptors and otherwise may not activate adenosine receptors. Given that adenosine (A) is a nucleotide base complementary to thymidine (T) and uridine (U), when a T appears in the DNA or a U in the RNA target, the anti-sense oligo will have an A at the same position.

Page 38, first sentence of 2nd. full paragraph, amend as follows:

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 60 nucleotide long which comprises the selected fragment and has a [C and G] T and U nucleic acid content of up to and including about 15%.

REMARKS

THE PENDING CLAIMS

Claims 108-131, 133-134, 146, 148, 151-156, 158-159, 161-173, 178-181, 183-189, 191-193, 195-198 and 200-234 are pending in this case, and no claims are being amended hereby.

THE AMENDMENTS TO THE SPECIFICATION

The present amendments are necessary due to typographical/clerical errors incurred at the time of filing at page 37 and original claim 89. From the context, it may be surmised that in order for an anti-sense oligonucleotide to have an adenosine (A) base at a specific site, the target nucleic acid must have at the site a thymidine (T) if it is DNA, or a uridine (U) if it is RNA.

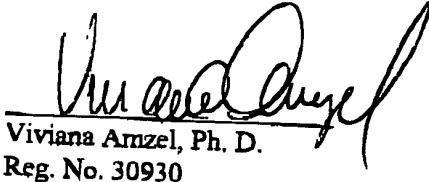
Further support for these amendments may be found in the same paragraph bridging pages 37 and 38, in the definition of universal bases that are provided to be substituted for adenosine (A) in the anti-sense oligonucleotide. These universal bases are said to "bind to thymidine (T) but lack the ability to activate adenosine receptors and otherwise may not activate adenosine receptors."

The applicant requests consideration of the present amendments to the specification and is providing substitute page 38 for printing purposes.

PATENT

In view of the foregoing amendments and remarks, and of the prior filing of a Substitute Sequence Listing and Declaration, as well as a Petition for Extension of Time and a Notice of Appeal with payment of the requisite fees, this application is believed to be in condition for examination and allowance. Early notice to this respect is solicited.

Respectfully submitted.
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S:\legal\00672\Amendment 01-5-24 II Supplements

genes, RNA and flanking regions that are devoid, or have a low T/U content, or alternatively one or more of the adenosine(s) present in the oligonucleotide(s) are substituted with other nucleotide bases, so called universal bases, which bind to thymidine (T) but lack the ability to activate adenosine receptors and otherwise may not activate adenosine receptors. Given that adenosine (A) is a nucleotide base complementary to thymidine (T) and uridine (U), when a T appears in the DNA or a U in the RNA target, the anti-sense oligo will have an A at the same position.

The method of the present invention may be used to treat ailments associated with or causing bronchoconstriction, allegy(ies) and/or inflammation associated with any of the diseases and conditions described above in a subject, regardless of its cause. The anti-sense agent(s) of the invention have preferably a low (or reduced) A content to prevent its liberation upon in vivo degradation of the agent(s), preferably up to about 15%, more preferably up to about 10%, still more preferably up to about 5%, and even more preferred being devoid of A ("desadenosine oligos").

The oligos of this invention may be obtained by first selecting fragments of a target nucleic acid having at least 4 contiguous nucleic acids selected from the group consisting of G and C, and then obtaining a first oligonucleotide 4 to 60 nucleotide long which comprises the selected fragment and has a T and U nucleic acid content of up to and including about 15%. The latter step may be conducted by obtaining a second oligonucleotide 4 to 60 nucleotide long comprising a sequence which is anti-sense to the selected fragment, the second oligonucleotide having an adenosine base content of up to and including about 15%. This method may also comprise, when the selected fragment comprises at least one thymidine base, substituting an adenosine base in the corresponding nucleotide of the anti-sense fragment with a universal base selected from the group consisting of heteroaromatic bases which bind to a thymidine base but have antagonist activity and less than about 0.3 of the adenosine base agonist activity at the adenosine A₁, A_{2b} and A₃ receptors, and heteroaromatic bases which have no activity or have an agonist activity at the adenosine A_{2a}.